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Comparative Efficacy of Antidiarrheal Activity of Racecadotril vs. *Mebarid*, an Ayurvedic Antidiarrheal Formulation in Children with Acute Diarrhea.

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ABSTRACT

In clinical practice, nonspecific antidiarrheals (allopathic and ayurvedic) are most commonly used by clinicians along with routine treatment to hasten the recovery and to give psychological reassurance. Although they are used extensively in practice, studies comparing their efficacy are few. This prospective observational study was carried out at two private clinics run by pediatricians to compare the efficacy, safety, and tolerability of racecadotril versus *MEBARID*, an ayurvedic polyherbal antidiarrheal formulation in the treatment of acute diarrhea. Children aged 2 y to 10 y who presented to the clinic with acute diarrhea and fulfilling selection criteria were enrolled and divided into two treatment groups viz, racecadotril and *MEBARID*. Data collection was done using predesigned case report forms and questionnaires. Outcome Measures used were 1)Duration of diarrhea after initiation of treatment 2)Frequency of stools until recovery 3)Time required for improvement in stool consistency. The groups were comparable clinically and demographically at enrolment. There was no significant difference in time needed for improvement in stool consistency with both racecadotril and *MEBARID* (17.76h vs.18.60h).Patients on racecadotril passed 3.32 ± 0.15 stools before recovery, while patients on MEBARID passed 3.13 ± 0.13 stools. The mean duration of treatment was less for racecadotril group (28.68 ± 2.18h Vs. 37.60 ± 2.18h; $P = 0.005$). Rapid improvement in stool consistency and frequency was found with both drugs. Thus racecadotril and *MEBARID* are rapid, equally effective treatments for acute diarrhea in children, but racecadotril significantly reduces the duration of diarrhea compared to *MEBARID*.

Keywords : Acute diarrhea, Mebarid, Racecadotril, Nonspecific antidiarrheals, Children

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INTRODUCTION

Acute diarrhea is major cause of childhood morbidity and mortality.[1] It is also a cause of anxiety and economic burden to parents of affected children. It is mostly infectious in origin and according to World Health Organization (WHO), infectious diarrhea accounts for nearly 3.2 % of all deaths globally. In developing countries, in which the toll of diarrhea is highest, poverty also adds an enormous additional burden, and long-term consequences of the vicious cycle of enteric infections, diarrhea, and malnutrition are devastating.

Acute diarrhea is defined as history of at least three loose or watery or unformed stools in a minimum period of 24 hours and usually for the duration of less than 7 days.[2] Acute diarrhea in children is very often self-limiting within few days. [3]

Antibiotics have a very limited role and do not alter the course of illness.[4,5] However, children are in danger of developing dehydration and complications. Therefore, an effective anti-diarrheal treatment would be beneficial. ORS forms mainstay in treatment of diarrhea; [6] but ORS does not reduce frequency & volume of stools or the duration of diarrhea. Hence, in clinical practice, nonspecific antidiarrheals like racecadotril and *MEBARID* (allopathic and ayurvedic) are most commonly used by clinicians along with routine treatment so as to hasten the recovery and to give psychological reassurance to patients / parents.[7,8,9]

Encephalins are endogenous opioid peptides that function as intestinal neurotransmitters. Inhibition of intestinal secretions is one of their actions. Racecadotril is a specific enkephalinase enzyme inhibitor that exhibits intestinal antisecretory activity without affecting intestinal transit, that is gut motility. It is the most widely used nonspecific antidiarrhoeal in children , and is an effective and safe treatment for acute diarrhea in children.

Although several studies about this drug have been reported in the literature comparing its efficacy with loperamide, no study has been reported in our country comparing its efficacy with *MEBARID*,a commonly used antidiarrheal in clinical practice [7] ; so this study was designed to compare the efficacy, safety and tolerability of racecadotril with *MEBARID* in the treatment of acute diarrhea in children.

MEBARID (Table 1) is a polyherbal preparation by S.G .Phyto Pharma (P) Ltd., is available in liquid dosage form suitable for children. Its efficacy and safety in children has been confirmed in our previous study.[10] This study was conducted to compare the efficacy, safety, and tolerability of racecadotril versus *MEBARID* in the treatment of acute diarrhea in children

Table 1: Composition of *MEBARID*

No.	Ingredients	Quantity (mg/10ml)
i	*Bael*	*100*
ii	*Ajmoda*	*100*
iii	*Lodhara*	*100*
iv	*Dadim*	*100*
v	*Badishep*	*100*
vi	*Daruhalad*	*100*
vii	*Jaiphal*	*50*
viii	*Sunth*	*50*
ix	*Ativish*	*50*
x	*Kuda*	*50*
xi	*Sugar*	*q.s*

MATERIALS AND METHODS:

Setting:

This was a prospective, observational study done in clinical settings for a period of 18 months. Two private clinics, run by registered medical practitioners (pediatricians),were selected after obtaining their informed written consent. The study protocol was approved by Institutional Ethics Committee of MIMER Medical College, Talegaon, Pune.

Study Population:

Children suffering from acute diarrhea presenting with 3 or more unformed stools in 24 hours and fulfilling the selection criteria were enrolled in the study. Informed written consent was obtained from one of the parents. They were divided into two treatment groups- Racecadotril and *MEBARID* at the discretion of pediatrician. Both groups were treated with routine antidiarrheal drugs, while racecadotril group received racecadotril in addition, *MEBARID* group received *MEBARID* in addition. Baseline demographic and clinical characteristics were recorded. Following baseline data were collected :

- Age, weight, height, immunization status, history of fever, vomiting, degree of dehydration
- (mild , moderate or severe) or other symptoms, prior use of any medication were noted
- Duration of diarrhea, character of stool (watery, mucoid, bloody etc), consistency of stool, were noted. A child could be enrolled only once.

Selection criteria:

Inclusion Criteria for enrollment was as follows:

1. Children of age 2 - 10 years, irrespective of their body weight were included except those severely malnourished (<50% of expected weight for that age)according to IAP criteria.

2. Acute Diarrhea of varied etiology
3. Duration of diarrhea of less than 2 days.
4. Diarrhea with co - morbidity which is not severe.

Children were excluded from the study based on following criteria :

1. Children less than 2 yrs and above 10 yrs.
2. Chronic, iatrogenic or bloody diarrhea.
3. Children with severe diarrhea and severe dehydration.
4. Children with severe malnutrition.
5. Children receiving antibiotics, pre/probiotics and/or zinc supplements or any other nonspecific anti-diarrheal drug.
6. Child with any other significant systemic illnesses

Data collection and data analysis

Patients of acute diarrhea attending the clinic were intervened by the pediatrician first. Case history was recorded followed by general examination and systemic examination.Prescription audit was conducted and prescription was analyzed in detail. Administration of concomitant medications such as antipyretics, antiemetics were recorded. Parents of children were informed in detail the study protocol in simple and lucid language.

A questionnaire was provided to parents and they were instructed to fill and record the details of the diarrheal episodes till recovery.

All the information was recorded in a predesigned CRF (Case Report Form) including the details of treatment drugs, which was filled on enrollment day in detail and on follow up days. Follow up was done on 3rd,5thand 7th day of treatment. In cases of failure to follow up, personal visit was done by investigator. A telephonic check was carried out daily. Any episode of complication, adverse effect or need for unscheduled use of IV fluids was recorded. Parents were sensitized to report the adverse effects like abdominal distension, drowsiness, lethargy, vomiting or constipation as early as possible.

Outcome variables

Efficacy criteria:

1. The primary efficacy criterion was duration of diarrhea- time between initiation of treatment and production of the final diarrheal stool.[11]
2. Secondary efficacy criteria consisted of frequency of stools after initiation of treatment until recovery and time needed for improvement in stool consistency.[12,13]Tolerability and safety were evaluated by recording the adverse effects experienced during treatment.

Recovery was defined as

1.Production of two consecutive normal stools

2.Production of one normal stool followed by 12 hours with no stool production.

3.No stool production for a period of 12 hours

Statistical analysis:

Statistical analysis was done using Student's unpaired "t" test. All the values are expressed as mean ± SEM. P<0.05 was considered as significant.

RESULTS AND DISCUSSION:

Total 110 children were enrolled, 50 in racecadotril group and 60 in *MEBARID* group.Both the groups tolerated the treatment well and continued the medications as advised till the end of treatment. Compliance in our study was quite good.The base-line parameters are shown in Table 2.There was no significant difference between two groups.

Table 2: Base-line parameters of patients on enrolment

Particulars	**Racecadotril**	***MEBARID***
Number	50	60
Age (y)	4.30 ± 0.32	4.20 ± 0.25
Sex (M:F)	27:23	33:27
Dehydration		
No Dehydration	18	23
Mild Dehydration	24	27
Moderate dehydration	08	10
Duration of diarrhea before enrolment (h)	36 ± 2.16	40.32 ± 2.16
Frequency of stools/day	5.22 ± 0.23	5.25 ± 0.24
Vomiting (No.of children)	14	11
Fever (No.of children)	09	06

Values are mean ± SEM

Table 3:Efficacy of racecadotril and *MEBARID*

Group	**Racecadotril (n=50)**	**Mebarid (n=60)**
Time(h) needed for improvement in stool consistency	17.76 ± 1.51	18.60 ± 1.30
Stool frequency	3.32 ± 0.15	3.13 ± 0.13
Duration of diarrhea (h)	28.68 ± 2.18 ***	37.60 ± 2.18

Values are mean ± SEM

*** *P<0.05* compared with *MEBARID.*

Assessment of efficacy:

There was no significant difference in time needed for improvement in stool consistency with both racecadotril and *MEBARID* (17.76h vs.18.60h). Reduction in frequency of stools in both

groups was comparable. Patients on racecadotril passed 3.32 ± 0.15 stools before recovery, while patients on *MEBARID* passed 3.13 ± 0.13 stools. No statistically significant difference was noted between two groups. The mean duration of treatment was less for racecadotril group (28.68 ± 2.18h Vs. 37.60 ± 2.18h)(Figure 3). Addition of racecadotril was found to reduce the duration of diarrhea significantly (Table 3, Figure. 1 , 2 & 3).

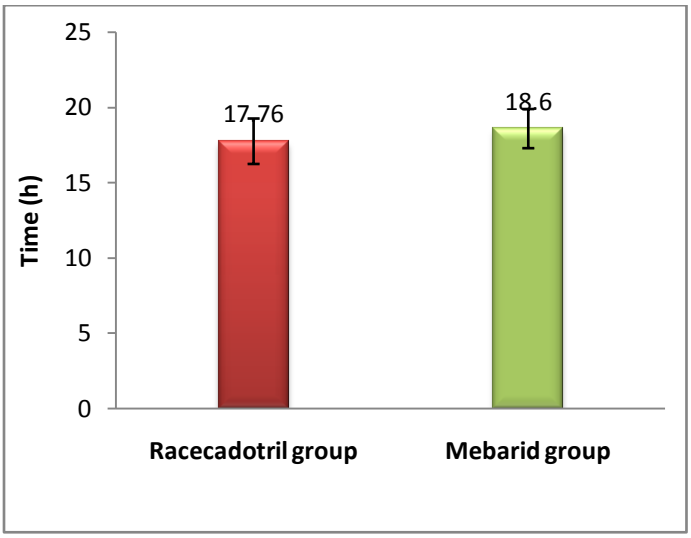

Figure 1. Time (h) required for improvement in stool consistency

Error bars represent the mean ± SEM

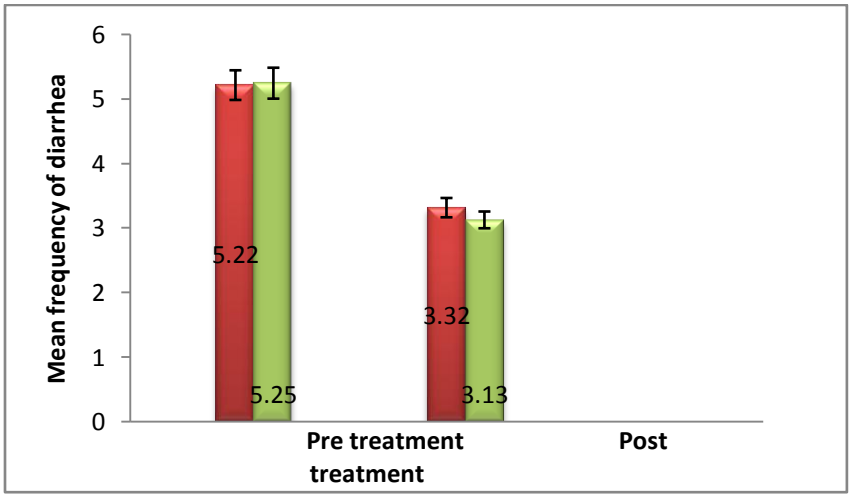

Figure 2. Mean±SEM number of stools passed by patients of racecadotril group (n=50) and *MEBARID* group (n=60) during the 24 hours before treatment commenced and from the start of treatment until recovery.

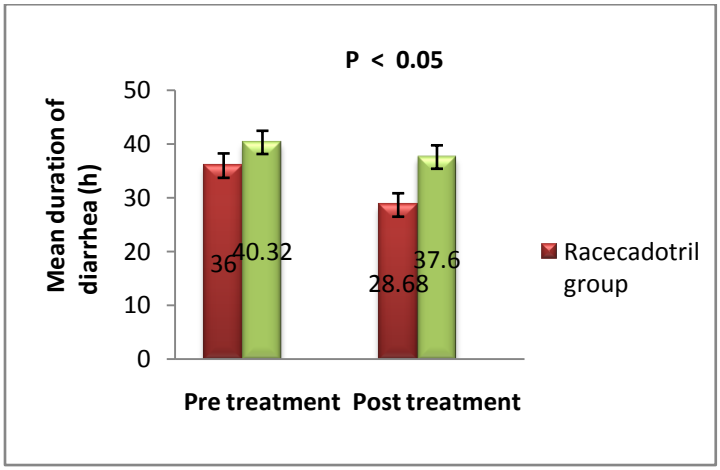

Figure 3. Mean duration of diarrhea before and after treatment in racecadotril group(n=50) and *MEBARID* group(n=60). Error bars represent the mean ± SEM.

Safety evaluation: Of 110 patients studied, no severe adverse events were observed in children. 5 patients from *MEBARID* group and 6 patients from racecadotril group complained of abdominal pain which was relieved by appropriate drugs. Initially 15 patients had fever on enrolment, which was cured by the second or third day of treatment with analgesics. (Table 1). 25 patients had vomiting along with diarrhea which was cured by day 3 with antiemetics.3 patients on *MEBARID* and 2 patients on racecadotril needed admission and IV fluids due to dehydration.1 patient from racecadotril group developed mild rash and complained of itching and was cured by day 5 with antihistaminic. No serious adverse effects were recorded during the study.

Present study examined several aspects of racecadotril and *MEBARID* supplementation. Moreover, the stool consistency and frequency, which are primary concerns of the mother are taken care of by both these drugs. Racecadotril and *MEBARID* resolved the symptoms of acute diarrhea rapidly and effectively. A decline in the number of loose stools and an increase in solid bowel movements was noted within 24 hrs after the initial visit in both groups.No significant differences were found in the number of bowel movements between the 2 groups after initiating treatment. As is seen that the diarrheal duration was comparable in both groups initially, but after treatment, racecadotril supplemented group has shown faster recovery. The duration of diarrhea was significantly shorter with racecadotril (28.68h; P = 0.005). Whereas the duration of diarrhea was not altered by addition of *MEBARID* to the routine therapy. However suffering of mothers and caretakers may be reduced to a great extent even by small improvement in symptoms by supplementation of *MEBARID*. Difference in two groups is probably because of presence of multiple ingredients in *MEBARID* having multiple actions in contrast to racecadotril which has specific action.

The results obtained in the present open label study are preliminary in nature and require further scientific studies with larger sample size. This study did not take into consideration other associated symptoms.

CONCLUSION:

Rapid improvement in stool consistency and frequency was found with both drugs. Thus racecadotril and *MEBARID* are rapid, equally effective treatments for acute diarrhea in children, but racecadotril significantly reduces the duration of diarrhea compared to *MEBARID.*

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